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09/580,797	05/30/2000	Peter C. Iwen	UNMC-Iwen	1242

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/580,797	Applicant(s) IWEN ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5 and 20-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5, 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed May 28, 2002. Currently, claims 2-5, 20-22 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's arguments and amendments to the claims.

3. This action contains new grounds of rejection necessitated by amendment.

New Grounds of Rejection Necessitated by amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Newly Amended Claims 2-4, and Newly added Claims 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over White et al. (PCR Protocols: A Guide to Methods and Applications, page 315-322, 1990) and Beck (US Pat. 5,827,695, October 1998) in view of Borsuk et al. (Acta Biochimica Polionica, Vol 41, No. 1, page 73-77, 1994) and Nikkuni et al. (J. Gen. Appl. Microbiol. Vol 44, Page 225-230, pages 225-230, 1998) and Pazoutova (Genbank Accession Number AJ001331, August 1997) and Peterson (Genbank Accession Number U65306, January 1998) and Aguirre et al. (Genbank Accession Number U93683, May 1997) and further in view of Sandhu et al. (US Pat. 5,707,802, January 1998).

It is noted that SEQ ID NO: 1 of the instant invention is identical to the ITS5 primer of White. Additionally, SEQ ID NO: 2 of the instant invention is 13 nucleotides upstream, within the 28S conserved region, of the ITS4 primer of White.

White teaches the structure of the fungal nucleic acid (Figure 1). It is noted that White teaches ITS1 and ITS5 are located in the small rDNA, and ITS4 is located in the large rDNA which would allow PCR amplification of both the ITS1 and ITS2 reigns which are highly variable among species. Table 1 provides the nucleic acid sequence of these probes. White specifically states that ITS primers make use of conserved regions of the 18S and 28S rRNA genes to amplify the noncoding regions between them (pg 320).

Beck teaches that the state of the art with respect to obtaining ITS regions of fungal species is high and aligning the sequences to design primers which are either generic to all fungal species or alternatively species specific is routine. Beck teaches that fungal rRNA genes are organized in units, each of which encodes three mature subunits of 18S, 5.8S and 28S. These subunits are separated by two internal transcribed regions, ITS1 and ITS2. The ITS sequences are particularly suitable for the detection of specific pathoytpes of different fungal pathogens. Beck teaches that methods to clone the ITS DNA sequences are known in the art as well as general isolation of DNA from fungal isolates (col. 5, lines 12-15). Beck teaches that ideally, primers to PCR amplify the entire ITS region were designed according to White (1990).

Neither White nor Beck specifically teaches using a primer of the instant SEQ ID NO: 2 for detecting Aspergillus in clinical samples.

However, Borsuk et al (herein referred to as Borsuk) teaches the ITS1 and ITS2 regions of three *Aspergillus* species, namely *A. awamori, A. wentii, A. nidulans*, as well as partial 18S, 5.8S and 26S rRNA. As seen in the alignment of Figure 1 and 2, the 26S region of rRNA is conserved among each of the strains.

Nikkuni et al (herein referred to as Nikkuni) teaches an alignment of the ITS region of 12 strains of Aspergillus. As seen in the alignment, the 28S region is conserved between all of the strains such that the region would be an ideal target for primers indented to amplify each of the fungal species. Nikkuni teaches that it is known "that rDNA ITS are highly divergent in *Fusarium sambucinum* and their sequencing provides good reliability in the detection of close phylogentice distance. Nikkuni

teaches that nucleic acid was isolated from the fungi material in the sample (page 226, col. 1). Nikkuni teaches that the nucleic acid was amplified using primers ITS4 and ITS5 as provided by White (1990) and sequenced. Nikkuni teaches that the Its regsions of these 12 strains were reproducibly amplified by using the primer pairs of ITS4 and ITS5 (pg 227, col. 2). Nikkuni also teaches that the sequences of ITS regions could distinguish the strains (pg 229, col. 1)(limitations of Claim 20).

Pazoutova teaches a nucleic acid sequence from *Aspergillus terreus* which contains the 5.8S rRNA gene and ITS1 and ITS2 DNA. The nucleic acid sequence contains SEQ ID NO: 2.

Peterson teaches a nucleic acid sequence from *Aspergillus niger* which contains the ITS1, 5.8S rRNA, ITS2 and 25S rRNA partial sequence. The nucleic acid sequence contains SEQ ID NO: 2.

Aguirre et al (herein referred to as Aguirre) teaches a nucleic acid sequence from *Aspergillus fumigatus* which contains 5.8 S rRNA, the ITS2 region and 28S rRNA. The nucleic acid sequence contains SEQ ID NO: 2.

Moreover, Sandhu et al (US Pat. 5,707,802) teaches detecting of fungi that cause disease in humans and in animals including A. flavus, fumigatus, niger, terreus (abstract). Sandhu teaches that Aspergillus fumigatus is among the top three causes of systemic fungal infection treated in hospitals (col. 2, lines 6-8). Sandhu also teaches that accurate detection of the Aspergillus species, fumigatus, flavus, nidulans, niger, terreus among others, represent a majority of Aspergillus species see in clinical specimens and their presence can cause diagnostic difficulties. Example 2 teaches

testing clinical specimens for specific fungal organisms which extracts DNA from clinical samples, PCR amplifies the samples, and then hybridizes the PCR amplified DNA with radioactively labeled species specific probes (col 37). Sandhu teaches that the aligned sequences contain sufficient variability to enable a person versed in this art, to develop additional species specific hybridization probes in the 10-50 nucleotide length or longer encompassing 200+ nucleotide lengths (col. 12, lines 50-60)(limitations of Claim 4).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of White and Beck given the specific sequences for *Aspergillus* as taught by Borsuk, Nikkuni, Pazoutova, Peterson and Aguirre in view of Sandhu which teaches Aspergillus is a clinically important fungus. As stated previously, it is noted that SEQ ID NO: 1 of the instant invention is identical to the ITS5 primer of White. Additionally, SEQ ID NO: 2 of the instant invention is 13 nucleotides upstream, within the 28S conserved region, of the ITS4 primer of White. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed methods using SEQ ID NO: 2 simply represents functional equivalents of the previously disclosed universal primer ITS4 as taught by White, a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties. SEQ ID NO: 2 of the instant invention is prima facie obvious because SEQ ID NO: 2 and the ITS4 are considered functional equivalents such that both SEQ ID NO: 2 and ITS4 are located within the conserved 28S region of the fungal pathogens. The art teaches alignments of *Aspergillus* species which clearly indicates that the region targeted by SEQ ID NO: 2 is conserved among the species. The art also provides additional *Aspergillus* species which include SEQ ID NO: 2 indicating that SEQ ID NO: 2 would be conserved among *Aspergillus* species. Further, SEQ ID NO: 2 and ITS4 would both amplify the entire ITS1 and ITS2 hypervariable region. Thus, SEQ ID NO: 2 is equivalent in function to ITS4.

It would have been further obvious to have detected the Aspergillus species within a clinical sample because, Sandhu teaches detecting of fungi that cause disease in humans and in animals including A. flavus, fumigatus, niger, terreus (abstract). Sandhu teaches that Aspergillus fumigatus is among the top three causes of systemic fungal infection treated in hospitals (col. 2, lines 6-8). Sandhu also teaches that accurate detection of the Aspergillus species, fumigatus, flavus, nidulans, niger, terreus among others, represent a majority of Aspergillus species see in clinical specimens and their presence can cause diagnostic difficulties. Therefore, it would have been obvious to have detected Aspergillus in clinical samples for the expected benefit of detecting infection in patients such that appropriate treatments may be provided.

The specification clearly states, on page 19, that the primers of the instant invention are "modifications of the original primers as stated by Henry (J. of Clinical Microbiology, Vol 28, No. 4, page 1510-1515). Henry teaches using primers of White. The specification teaches that these modifications were made to optimize the amplification procedure. However, as noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the probe selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Response to Arguments

The response traverses the rejection. The response asserts that the obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. This argument has been reviewed but is not convincing because the instant combination of references which has been relied upon provides clear suggestion that primers which flank the ITS regions are ideal to compare divergences between the species which will allow for different species and/or strains to be distinguished. The ordinary artisan would have recognized based upon the alignments in the art teaching conserved regions flanking the ITS2 region that alternate primer sequences may be used to amplify the ITS1 and ITS2 regions. Any primer designed to the conserved

regions among the Aspergillus strains would have the expected benefit of amplifying the Aspergillus species for further differentiation. The instant SEQ ID NO: 2 and the ITS4 taught by White and utilized throughout the art are functional equivalents which have the same function of amplifying the ITS1 and ITS2 regions of Aspergillus. Therefore, as taught by Beck, primers can be designed to regions highly conserved among the species to develop genus-specific primers (col. 5, lines 45-50). Therefore, designing primers to the conserved regions of the conserved regions 3' of the ITS2 region would have been obvious.

The response has amended to claims to be directed to a patient sample. At the time the invention was made, it was well known that Aspergillus species were involved in clinical specimens and linked to disease in humans. Therefore, the rejection has been modified above to reflect the amendment of detecting the fungal species in a patient sample.

The response argues that "the examiner's assertion that SEQ ID NO: 2 is a structural homolog of the ITS4 sequence of White et al. flies in the face of the patent office position that each nucleic acid sequence is a separate and distinct invention" (page 10 of the response). This argument has been thoroughly reviewed but deemed non persuasive. It is noted that the instant rejection is an obviousness rejection and not a restriction requirement. Restrictions are based upon separate and distinctness between the claims provided in an application. Obviousness rejections are based upon the prior art and whether given the prior art the skilled artisan would be motivated to have modified the teachings in the art for a benefit. The instant application has not

restricted between ITS4 and the instant SEQ ID NO: 2. There is no assertion that ITS4 and SEQ ID NO: 2 are separate and distinct inventions. The full ITS regions were known in the art. Sub-seqeuences of these Aspergillus nucleic acids have not been considered distinct over the full length. Therefore, the use of the ITS4 primer and the full length ITS regions in considering obviousness of the instantly claimed SEQ ID NO: 2, is not precluded.

The response asserts that the examiner is "relying on disclosure of full length sequences that include, but do not teach, or suggest SEQ ID NO: 2". This argument has been thoroughly reviewed, but found unpersuasive because as reiterated above, there is specific motivation, suggestion and teachings that fungal primers designed to highly conserved regions allow development of genus specific primers. The instant primers, like the primers taught in the art are designed to highly conserved regions. The ordinary artisan would have an extremely high expectation for success that any primer to a highly conserved region between species could be used as a genus specific primer.

The response asserts that "the applicant's primer set is unique". This argument has been reviewed but not convincing because it is noted that the primer set is not anticipated. However, the rejection of record is an obviousness rejection which does not require that the art teach the claimed invention, rather the rejection requires that the claimed invention is obvious given the teachings in the art.

Thus for the reasons above and those already of record, the rejection is maintained.

6. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over White et al. (PCR Protocols: A Guide to Methods and Applications, page 315-322, 1990) and Beck (US Pat. 5,827,695, October 1998) in view of Borsuk et al. (Acta Biochimica Polionica, Vol 41, No. 1, page 73-77, 1994) and Nikkuni et al. (J. Gen. Appl. Microbiol. Vol 44, Page 225-230, pages 225-230, 1998) and Pazoutova (Genbank Accession Number AJ001331, August 1997) and Peterson (Genbank Accession Number U65306, January 1998) and Aguirre et al. (Genbank Accession Number U93683, May 1997) as applied to Claims 2-4, 19 above, and further in view of Nelson et al (US Pat. 5,827,656, October 1998).

Neither White, Beck nor Borsuk, Nikkuni, Pazoutova, Peterson and Aguirre teach detection of more than one probe using either different signal moieties or separation moieties.

However, Nelson teaches a method for assaying a plurality of nucleic acid analytes suspected of being in a single sample by providing a plurality of probes with different labels and a sample, hybridizing and detecting (see Claim 1 of Nelson). Nelson teaches detection of pathogens. Moreover, Nelson teaches that the present invention provides rapid assay method for the detection of the presence of more than one species of organism in a test sample (col. 5, lines 45-48). Nelson teaches that the method allows for the simultaneous detection and quantification of more than one specific nucleic acid in a sample.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of White and Beck

given the specific sequences for Aspergillus as taught by Borsuk, Nikkuni, Pazoutova, Peterson and Aguirre in view of Nelson. The ordinary artisan would have been motivated to have used multiple signal moieties or solid supports for detection of more than one analyte simultaneously for the expected benefit of saving reagents, cost and time. Nelson teaches that the present invention provides rapid assay method for the detection of the presence of more than one species of organism in a test sample.

Response to Arguments

The response traverses the rejection. The response asserts that Nelson does not cure the deviciencies of White, Beck, Borsuk, Nikkuni, Pazoutova, Peterson, Aguirre. This argument has been reviewed but is not convincing because the arguments above were not found to be convincing. Applicant's have not separately argued the rejection of Nelson. Thus for the reasons above and those already of record, the rejection is maintained.

7. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over White et al. (PCR Protocols: A Guide to Methods and Applications, page 315-322, 1990) and Beck (US Pat. 5,827,695, October 1998) in view of Borsuk et al. (Acta Biochimica Polionica, Vol 41, No. 1, page 73-77, 1994) and Nikkuni et al. (J. Gen. Appl. Microbiol. Vol 44, Page 225-230, pages 225-230, 1998) and Pazoutova (Genbank Accession Number AJ001331, August 1997) and Peterson (Genbank Accession Number U65306, January 1998) and Aguirre et al. (Genbank Accession Number U93683, May 1997) and further in view of Sandhu et al. (US Pat. 5,707,802, January 1998) as applied to Claims 2-4, 20 above and further in view of Wang et al (US Pat. 5,876,977, March 1999).

Neither White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson, Aguirre nor Sandhu teach detection of fungal nucleic acids by restriction mapping.

However, Wang teaches the identification of ITS region s by amplifying and detecting discrete and species-specific RFLP patterns (abstract). Wang teaches that the method is reliable, highly sensitive, easy to interpret results and a definite way to identify similar nucleic acids, in addition to contamination (col. 6-7).

Therefore, the ordinary artisan would have been motivated to modify the detection method for PCR amplified ITS regions of White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson, Aguirre and Sandhu with the teachings of Wang. The ordinary artisan would have recognized the benefit of generating RFLP patterns based upon PCR amplified nucleic acids. Therefore, the ordinary artisan would have modified the PCR amplification followed by probe detection method of White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson, Aguirre and Sandhu with a RFPL analysis of the ITS regions for the expected benefits of reliability, sensitivity, definitiveness and ease taught by Wang.

8. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over White et al. (PCR Protocols: A Guide to Methods and Applications, page 315-322, 1990) and Beck (US Pat. 5,827,695, October 1998) in view of Borsuk et al. (Acta Biochimica Polionica, Vol 41, No. 1, page 73-77, 1994) and Nikkuni et al. (J. Gen. Appl. Microbiol. Vol 44, Page 225-230, pages 225-230, 1998) and Pazoutova (Genbank Accession Number AJ001331, August 1997) and Peterson (Genbank Accession Number U65306,

January 1998) and Aguirre et al. (Genbank Accession Number U93683, May 1997) and further in view of Sandhu et al. (US Pat. 5,707,802, January 1998) as applied to Claims 2-4, 20 above and further in view of Felgner et al (US Pat. 6,165,720, December 2000)

Neither White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson, Aguirre nor Sandhu teach detection of nucleic acids by fluorescent molecular probes.

However, Felgner teaches FISH (fluorescent in situ hybridization) requires the tissue to be fixed, sectioned and permeabilized (col. 19, lines 35-40). FISH is a method which directed fluorescent probes to specific region within a cell to be detected.

Therefore, the ordinary artisan would have been motivated to have modified the detection method for ITS regions of White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson, Aguirre and Sandhu with the teachings of Felgner. The ordinary artisan would have recognized the benefit of detecting nucleic acids in situ with out the need for extraction or amplification. Therefore, the ordinary artisan would have modified the PCR amplification followed by probe detection method of White, Beck, Borsuk, Polionica, Nikkuni, Pazoutova, Peterson, Aguirre and Sandhu with a rapid method of FISH which uses a fluorescent labeled probe for detection without the need for amplification or extraction. Therefore, the ordinary artisan would have been motivated to have used the FISH analysis method to avoid extraction and PCR amplification methods.

Conclusion

9. No claims allowable over the art.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Pauline Farrier, whose telephone number is (703) 305-3550.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
July 23, 2002

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600